Review Article

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Cancerogenesis in *Helicobacter pylori* infected stomach – role of growth factors, apoptosis and cyclooxygenases

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SUMMARY

Background: *Epidemiological and animal studies demonstrated a link between gastric cancer (GC) or mucosal associated lymphoid tissue (MALT) lymphoma and chronic infection with Helicobacter pylori (H. pylori). The exact mechanism responsible for the development of GC and MALT-lymphoma in H. pylori-infected patients still remains obscure. This report is designed to overview the molecular biology, especially the gene expression and histochemical manifestation of gastrin and other growth factors such as transforming growth factor alpha (TGFα) and hepatocyte growth factor (HGF) in the GC before and after eradication of H. pylori. Furthermore, gene expression of cyclooxygenase-1 (COX-1) and COX-2 and apoptosis-related proteins such as Bax and Bcl-2 are discussed.*

Material and methods: *The findings originate from two series of patients; Series I involving 337 GC patients and 400 age- and gender-matched controls and series 2 including 20 MALT-lymphoma patients and 40 matched controls.*

Results: *An overall H.pylori-seropositivity reached about 80% in GC and about 90% in MALT-lymphoma, significantly higher than in non-cancer controls (60%). The prevalence of CagA-positive strains was about twice as high (about 70%) in GC and MALT-lymphomas as in sex- and age-matched controls. Expression of gastrin was detected in antrum of all tested patients but also in majority (90%) of GCs and MALT-lymphomas tumor tissue. HGF and TGFα were expressed more frequently in GC tissue than in normal fundic mucosa. COX-1 was similarly expressed in GC and MALT as in intact mucosa, while COX-2 mRNA was detected only in tumor tissue, being attenuated by H.pylori eradication in GC and abolished by this therapy in MALT-lymphoma. The plasma levels of α-amidated gastrin in GC and MALT were several folds higher than in controls. Gene expression of bcl-2 was detected in all, while bax – only in about 50% of GC samples.*

Conclusions: *Infection with H. pylori, especially that expressing CagA-positivity, is primum movens in developing GC and MALT-lymphoma and the upregulation of growth factors, particularly of gastrin, and COX-2 and dysregulation of the Bax/Bcl-2 system seem to contribute to gastric cancerogenesis.*

BACKGROUND

Gastric cancer (GC) and MALT-lymphoma, the most common malignancies in the digestive system [1,2], are linked to *H. pylori* infection and develop almost exclusively in the stomach with atrophic gastritis and intestinal metaplasia or dysplasia caused by this infection (Fig. 1). The discovery of this infection is considered as one of the most important advances in gastroenterology at the turn of the 3rd millennium [3] and *H. pylori* has been classified in 1994 by the International Association for Research

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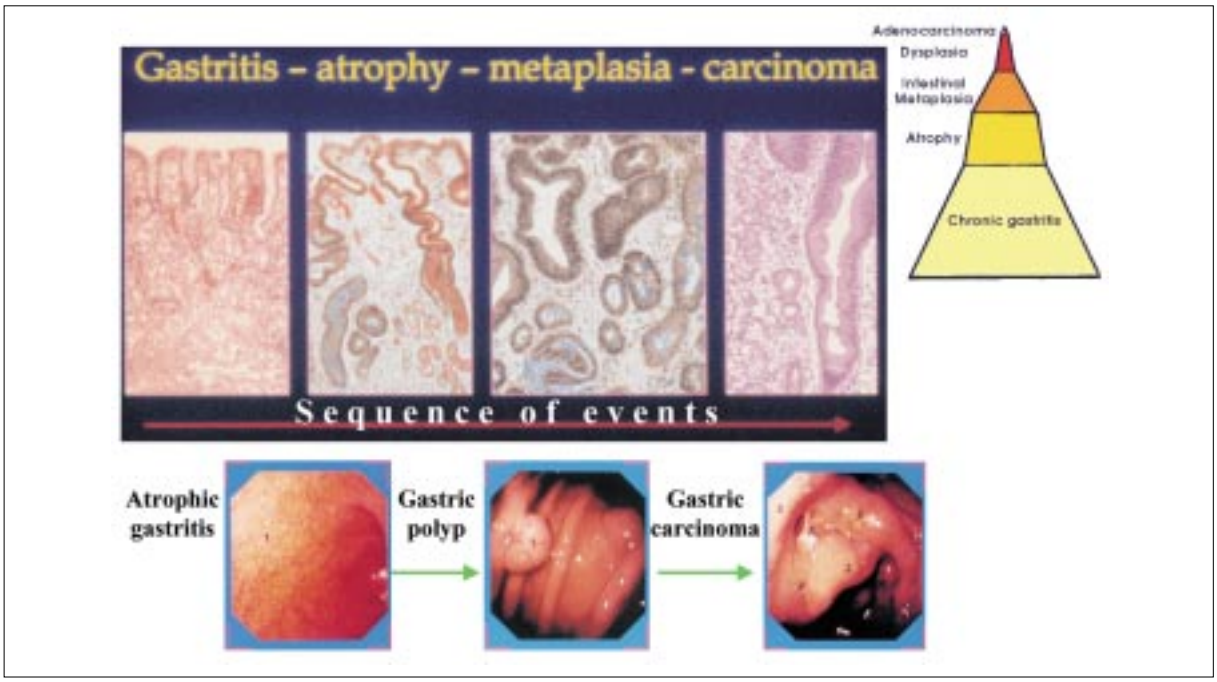

Figure 1. Sequence of histological and endoscopic events in *H. pylori* infected stomach with accompanying transformation of chronic atrophic gastritis to chronic active gastritis with polyp, intestinal metaplasia and dysplasia to cancer. The Burma's 'pagoda' illustrates the decreasing frequencies of chronic active gastrirtis through gastric atrophy, metaplasia, dysplasia and finally gastric cancer.

against Cancer (IARC) as a carcinogen type 1 for GC [4] and the cause of MALT-lymphoma [5].

H. pylori is probably the most common bacterial infection with a world-wide prevalence approximating 50% [6] (Fig. 2). Epidemiological reports [7,8] suggested and animal studies [9,10] confirmed that the chronic infection with *H. pylori* is an important risk factor for the development of GC. Infection with *H. pylori* alters many gastric factors that contribute to the pathogenesis of GC such as induction of atrophic gastritis with intestinal metaplasia and dysplasia, predicted by Correa et al, long before the discovery of *H. pylori* [11,12]. With the recognition of crucial role of *H. pylori* and gastrin upregulation as missing steps in cancerogenesis the so called Correa's cascade has to be accordingly modified (Fig. 3). This does not refute the significance of genetic component including polymorphism of interleukin (IL)-1 or rare hereditary diffuse gastric cancer [13] as well as the contribution of various carcinogenic factors including N-nitroso--compounds, reactive oxygen species, decreased vitamin C contents in gastric juice, increased epithelial cell turnover and others. [13–20].

The **1st or pre-initiation step in gastric cancerogenesis** results from the action of various environmental carcinogens including prolong exposure to microbial or viruses, contact with noxious chemicals or excessive radiation of gastric mucosal cells result in acquired (environmental) DNA damage. They cause the changes in the stability of the DNA and whole genome. At this step, the prevention of the exposition to the microbes or viruses, the reduction or avoidance of the contact with chemical such as e.g. smoking, decrease in the exposition to sun and increased intake of foods containing scavenges of reactive oxygen or nitrogen species (ROS) such as vegetables and fruits or supplementation with anti-oxidant vitamins A, C, D and E are the only ways of preventing further DNA damage and helping the recovery of the genes coding the enzymes repairing the existing DNA damage.

RESULTS AND DISCUSSION

The *H. pylori* IgG and CagA seroprevalence in gastric cancer patients, the initiation step of cancerogenesis

As described by Correa et al [21], long before the discovery of *H. pylori*, the development of GC is a multistep process in which environmental and genetic factors determine the transformation of normal gastric epithelial cells into metaplastic, dysplastic and finally malignant cells (see Fig. 3). The sequence of events from normal mucosa to atrophic gastritis with intestinal metaplasia (without or with gastric polyps) and fi-

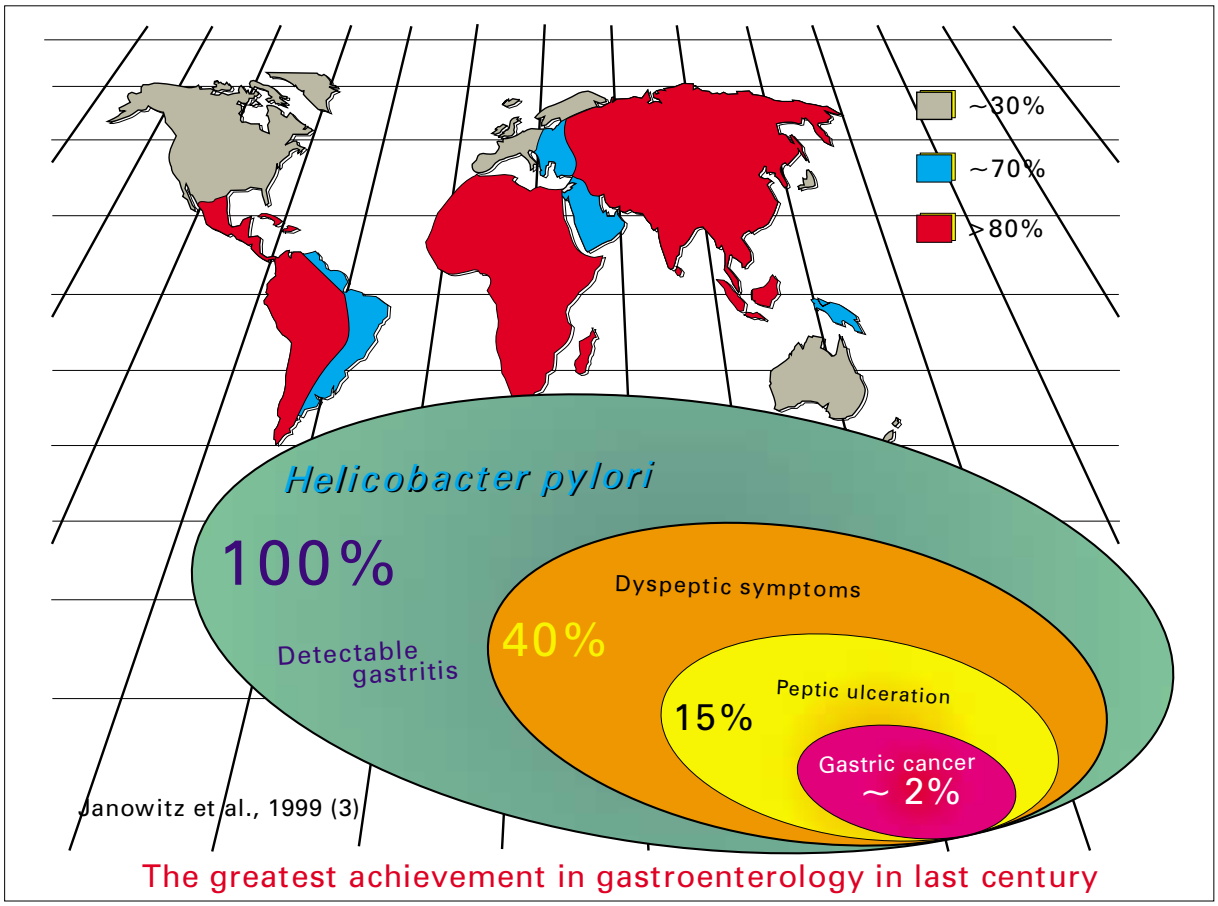

Figure 2. World distribution of *H. pylori* infection and its gastric consequences from common chronic gastritis (100% infected) to cancer (about 2%).

nally to GC or MALT-lymphoma, has been verified both endoscopically and histologically, but each step may take several years to develop through the initiation (step 2), progression (step 3) and spread (step 4) of cancer. In case of the *H. pylori* infection the initiation may occur even at younger age such as in Japan where the risk of GC expressed in term of odds ratio (OR) below 40 years reaches about 13 (95% CI: 5.3–36.0). There are conflicting data concerning the significance of the association of the GC with the *H. pylori* CagA status in Japan but, in contrast, an increased association of GC with the *H. pylori* CagA genotype was found in young Italian patients [23].

The most important for the **initiation step of cancerogenesis (step 2)** is the entrance of the cell into the mutation pathway, especially concerning the genes coding enzymes repairing DNA and genes suppressors of the neoplastic transformation. Among the more important events of this initiation step are; a) the activation of protooncogens such as K-ras, stimulating cell proliferation rather than their differentiation, b) the expression and release of gastrin as well as other growth factors by precancerous cells, c) the mutation of the suppressor genes such as p53, d) the dysregulation of apoptotic genes leading to the enhancement of activity of antiapoptotic gene such as *bcl-2* with the decline of proapoptotic genes such as *bax* with inhibition of apoptosis and e) the dysregulation of the DNA repair genes. These cells with mutation of certain genes are still stimulated to grow and proliferate by the same growth factors as normal cells i. e. gastrin and other growth factors (HGF and TGFα), acting by separate gastrin or growth factor receptors that can be identified using specific primers and RT-PCR or Western blot. Our studies using these techniques clearly demonstrated the existence of gastrin and its gastrin-receptors so called CCK_B-R and EGF-receptors (EGF-R) that transduce the action of these growth factors (produced in excessive amounts) through intracellular signaling enzymes starting with receptor-bound tyrosine kinase responsible for the phosphorylation of regulatory proteins of the activation of cell division, proliferation and tumor growth.

Our Polish study presented in abstract form [24] included 337 GC patients aging from 21 to 80 yrs with

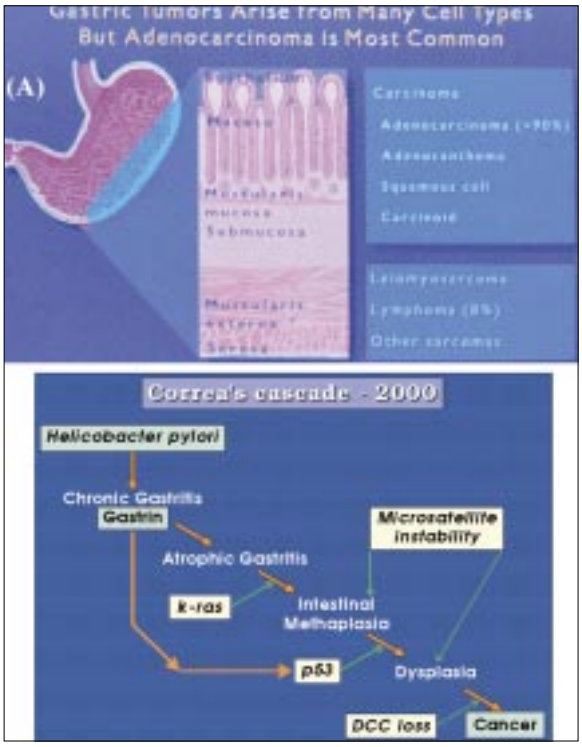

Figure 3. Modified 'Correa's cascade' including the role of *H. pylori*, gastrin and major oncogens (on left). Gastric tumors arise from various cells but most frequent adenocarcinoma originates from the neck mucous cells while MALT lymphoma – from lymphocytes in deeper wall layer.

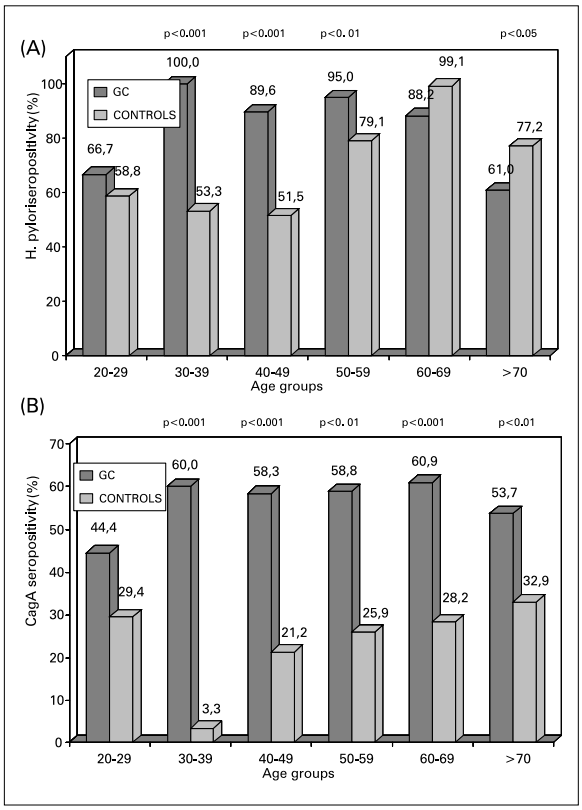

Figure 4. *H. pylori* seropositivity (upper panel) and CagA (lower panel) in GC patients and healthy controls at various age groups.

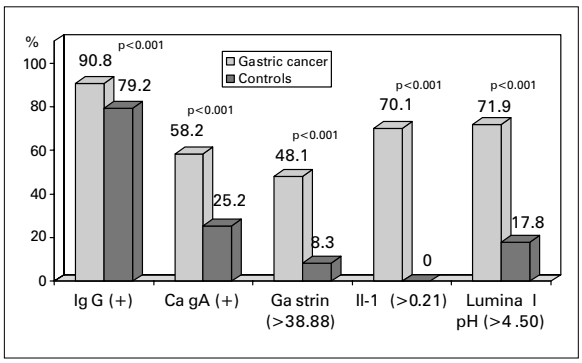

Figure 5. The overall percentage of *H. pylori* and CagA seropositivity, plasma gastrin, IL-1β, and luminal pH values above the cut-off points (calculated with ROC) in GC patients and healthy controls.

median age 59.4 yrs and 337 sex- and age--randomly selected controls, the overall *H. pylori* seropositivity was significantly higher (91%) than in controls (78%), while CagA seropositivity was roughly twice as high in GCs (59%) as in controls (25%). This difference in *H. pylori* IgG and CagA prevalence was observed at almost all tested age groups (Fig. 4). A summary OR (SOR) for *H. pylori* IgG in GC was about 2.6 reaching, like in Italian study, the highest value of 8.09 at the age 40–49. SOR for CagA averaged 4.1 supporting the notion that the risk of GC in *H. pylori* patients was markedly increased for infection with those bacteria that were CagA positive. The overall percentage of patients with positive *H. pylori* IgG, CagA and plasma gastrin, IL-1 and luminal pH above the cut-off values in GC and controls are shown on Fig. 5.

Role of growth factors in the initiation and promotion of gastric cancer and possible therapeutic application of anti-growth factors in the control of tumor cell growth

During the last decade, extensive studies have been performed to define the molecular mechanism underlying the progression from normal to malignant cells though the underlying molecular pathomechanism of GC and the exact role of *H. pylori* in carcinogenesis remain undetermined. There is an accumulating evidence that the transformation of the normal *H. pylori* infected gastric mucosal cells into the malignant cells and the development of GC require the action of mucosal growth promoting factors such as gastrin, HGF

and TGFα [8–20, 24–26]. The implication of α--amidated gastrin G-17 and G-34, as measured by radioimmunoassay, was reported by our group two years ago [19] using smaller number of patients, but now with 337 GC patients and 337 sex-, age-matched controls, we confirmed that mean values of plasma gastrin in GCs was significantly higher than that in controls. The area under the Receiving Operator Characteristics (ROC) curve was calculated to measure the discrimination power of various biomarkers such as *H. pylori* IgG, CagA, gastrin, IL-1α and intragastric pH showed that the best cut-off point was then calculated from this ROC curve was the plasma gastrin level above 38.9 pM, the intragastric acidity with pH above 4.50 and plasma IL-1α above 4.0. The SOR reached the highest value for gastrin in GCs, being about 10, reaching the peak value of about 15 at age 30–39 and for intragastric pH above 4.5 attaining about 8.0 (see Fig. 5). This study reinforced our notion that gastrin is the major factor implicated in *H. pylori* -related gastric carcinogenesis and that the measurement of plasma gastrin and intragastric pH in *H. pylori* infected patients provides the strongest discriminative diagnosis of GC. Our findings may have practical implication in screening cancer at earlier stage by using the approach similar to that of PSA (prostate specific antigen) in detection of prostate cancer. In case of GC simple measuring plasma gastrin, and gastric hypochlorhydria (by determination of plasma pepsinogen level which reflects quite well the gastric secretory and indirectly the atrophy status) in *H. pylori* seropositive may be useful in screening the GC at the preliminary stage. Further nation--wide study using these determination may prove usuful in detecting the precancerous stage or gastric malignancy.

There is also an evidence linking the upregulation of HGF, normally present in the gastric mucosa, to the development and progression of various epithelial and nonepithelial tumours [20,26–30]. Another mitogenic peptides, EGF and TGFα, that are also biosynthesised in the gastric mucosa, especially following its damage by *H. pylori*, elicit their biological action through interaction with cell-surface epidermal growth factor receptor (EGF-R) by activating its tyrosine kinase activity [31]. This interaction of growth factors also results in the induction of nuclear oncogenes such as c--myc, c-jun and c-fos to exert tumor cell growth--stimulating effect [32]. Different cancer cell lines co-express EGF and TGFα and EGF-R, suggesting that EGF and TGFα may also be implicated in the carcinogenesis, acting as autocrine growth factors [33]. Gene expression of HGF and TGFα was found to be increased in gastric mucosa colonized by *H. pylori*, reinforcing a possible link between these growth factors and *H. pylori*-associated gastritis and gastric carcinogenesis [18,24,33,34]. Serum TGFα was previously found to be elevated in GC patients and over-expression of this peptide was associated with an advanced stage of the cancer disease and poor prognosis [26]. It was suggested to be an useful marker of GC for predicting the progress of the disease and follow-up after surgery.

Among the growth factors, gastrin appears to be the most important gastrointestinal hormone involved in the stimulation of gastric acid secretion via activating the enterochromaffin-like (ECL)-cells and releasing histamine and in stimulating epithelial cell proliferation in the gastrointestinal tract, especially in the fundic and colonic mucosa [35]. *In vitro* studies have shown that gastrin stimulates the proliferation of gastric cancer cell lines through the induction of specific mitogen activated protein kinase [36]. Gastrin is mainly synthesized in antroduodenal G-cells but there is also an evidence that gastrin, especially α-amidated gastrin, may be produced in extra-antroduodenal areas, such as in some solid tumours originating from tissue, which normally express only negligible amount of gastrin, including pancreas, liver or bronchi, which embriologically originate from the same endoderm tube [37–39]. Chronic infection with *H. pylori* in GC patients has been shown to elevate the plasma gastrin level and to enhance the release of this hormone into the gastric lumen, where it may stimulate the growth of *H. pylori* and release of α-methyl-histamine that in turn activate the G-cells and cancer cells to produce more gastrin stimulating the growth of tumor cells. We showed that *H. pylori* eradication in GC patients shortly before the surgery was followed by a marked and immediate fall in plasma gastrin level, gastric luminal gastrin content and cancer tissue gastrin level (Fig. 6).

Treatment of growth factors–dependent gastric cancer

As examined *in vitro* isolated gastric mucous cells, we found that gastrin added to cell culture in combination with other growth factors (TGFα, HGF, EGF) induced by the *H. pylori* infection and/or mutated and hyperactive K-ras, causes an overexpression of p53 and this was followed by the phospho-

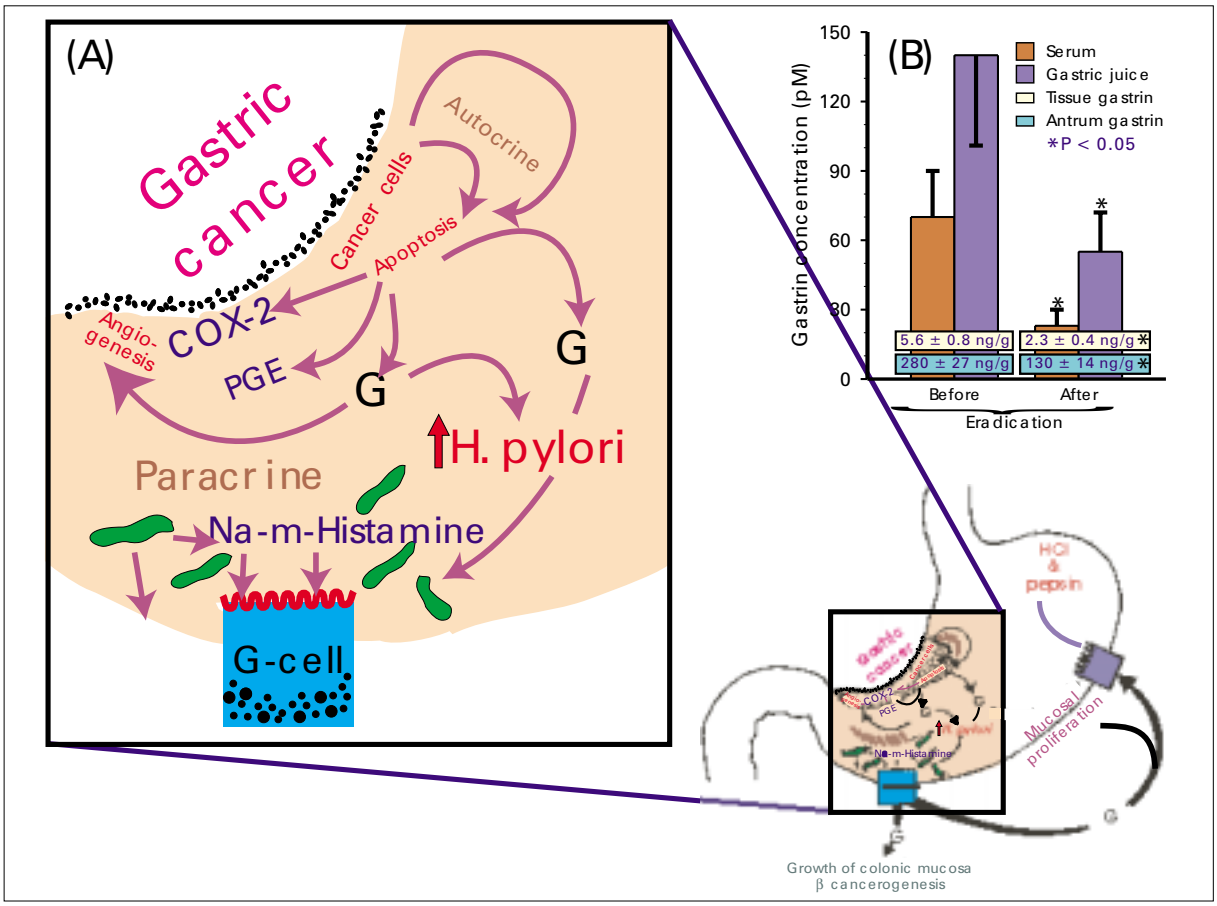

Figure 6. Schematic presentation of the proposal of important role of gastrin and *H. pylori* infection in gastric cancerogenesis (A). The eradication of *H. pylori* results in almost immediate reduction in gastrin release in these patients (B).

rylation and activation of MAP-kinases resulting in the activation of cell division and tumor growth are depicted on the Fig. 7.

In humans at this step of gastric carcinogenesis, the therapeutic approach should include first of all the eradication of *H. pylori* to reduce the production of major growth promoting factor of malignat cells such as gastrin. It may be worthwhile to mention that extensive program of *H. pylori* eradication as well as prolonged treatment of gastro-esophageal reflux with proton pump inhibitors (PPI) such as omeprazole without eradication of *H. pylori* not only results in the decline in the *H. pylori* prevalence but also 'shifts' the usual GC location in the distal stomach to its proximal part (body and *cardia*). This has been explained by the ascension of the bacteria (in PPI treated patients) from *antrum* towards the esophageo-gastric junction through the induction of atrophic gastritis in the corpus and cardia of the stomach [40].

Recently, the attempts have been made to neutralize gastrin produced by malignant cells with endogenously induced gastrin-neutralization antibodies in various gastric and colorectal cancers. These antibodies are produced by challenging body's immunological system with the complex of gastrin-17 (G-17) with diphteria toxin (G17DT). Such gastrin neutralizing antibody raised by immunization with G17DT, called gastrimmune (Afton, USA), has been tried with some success in prolonging the life of patients with gastric and colorectal cancers but these antibodies are capable of neutralizing only α--amidated G-17 (Fig. 8), but colorectal cancers produce mainly glycine extended gastrin and pro--gastrin [35,41], which are not recognized by these antisera and this explains the limited success of gastrimmune in treatment of these cancers. It is of interest that glycine-extended gastrin and progastrin exhibit a powerful tumor cell growth stimulatory activity without affecting gastric acid stimulatory action characteristic for G-17 [35,41].

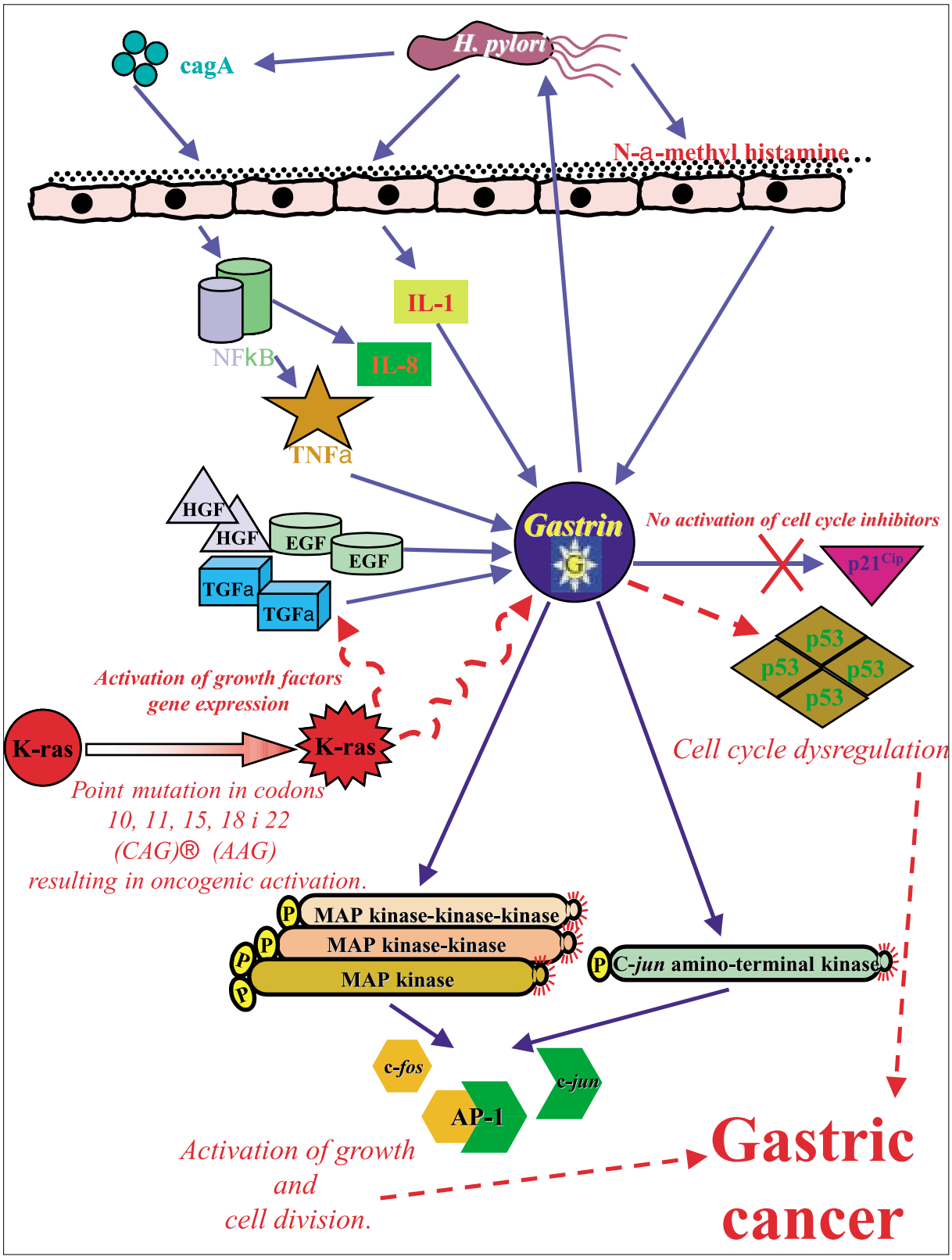

Figure 7. The important role of gastrin in gastric cancerogenesis (see text).

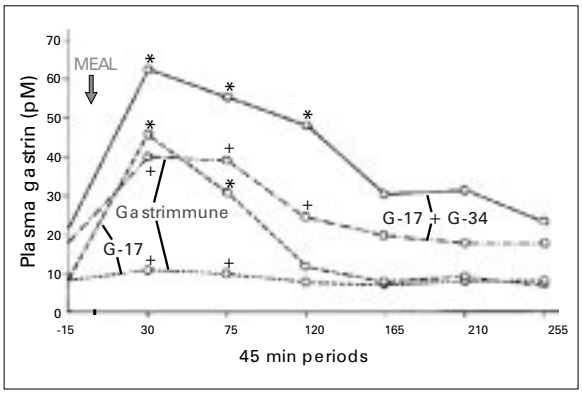

Figure 8. Plasma gastrin-17 and gastrin-34 in gastric cancer patients under basal conditions and after protein meal in gastric cancer patients before and after treatment with gastrimmune.

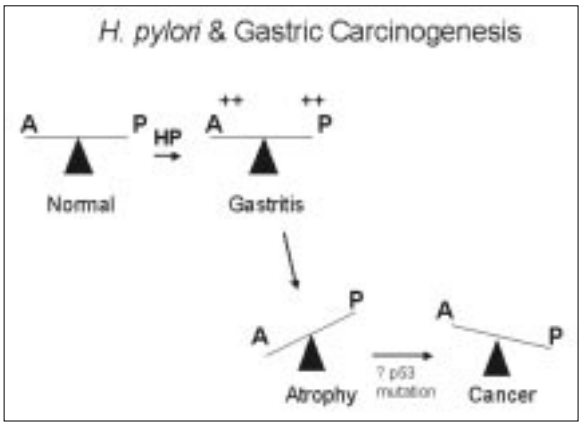

Figure 9. *H. pylori* infection and enhanced and inhibited apoptosis (A) and proliferation (P) leading to gastric cancer.

As mentioned before, in addition to gastrin, several other growth factors are generated by tumor cells and contribute to the stimulation of cancer cells *via* specific growth factor receptors such as EGF-R [20]. The antisera against the membrane receptors for EGF receptors (EGF-R) such as Herceptin (Genentech, USA), that block these receptors at the breast cancer cells, have been tried with some success [42]. The most effective was found an anti-growth agent, Glivec (Novartis, Germany), which cured myelogenous leukemia [43] and some stromal gastric tumors [44] blocking the intracellular signal pathways of growth factors. Various endocrine tumors such s gastrinoma can be successfully treated using octreotide (Novartis) that binds specific somatostatin-receptors (SST2-R), that are regularly present on the normal G-cells but also on the gastrin-producing cancer cells [45]. Many other anti--growth factors (e.g. IMC-C225 – Memorial Sloan Kettering) and anti-gastrin agents are now under active laboratory or clinical trials though they are

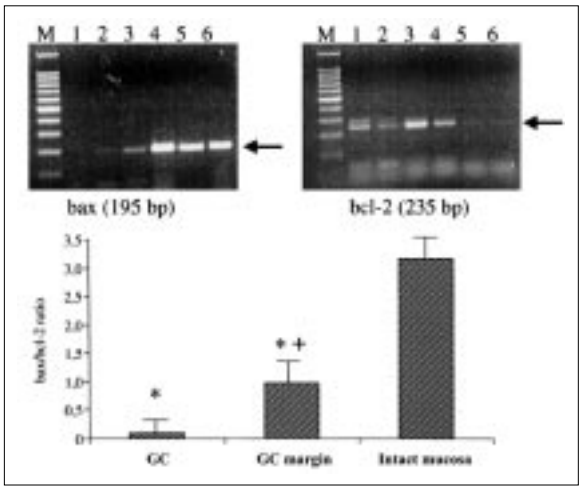

Figure 10. Expression of bax and bcl-2 in gastric cancer tissue, GC margin and intact mucosa

not expected to kill the cancerous cells but only to reduce or abolish their growth or to augment the anticancer efficacy of classic chemotherapy. Only Glevec has been approved by FDA for the treatment of chronic myelogenous leukemia [43].

Apoptosis, angiogenesis ans COX-2 expression

Recent studies have shown that the *H. pylori* infection first enhances both apoptosis (A) and mucosal cell proliferation (P) but shen chronic active gastritis becomes atrophic with intestinal metaplasia and dysplasia it disturbes balance between cell survival and (apoptosis) resulting in the dysregulation of the genes controlling the apoptosis that may be closely related to the cancer development (Fig. 9). The Bcl-2 family of proteins has been shown to be involved in the inhibition of the apoptosis [20,46, 47]. Some other members of this family of proteins, such as Bax, are promotors of apoptosis [47]. There is an evidence that tumor development is associated with the inactivation of Bax and with the over-expression of Bcl-2, leading to an overall inhibition of apoptosis [47]. The expression of apoptosis-related genes *bax* and *bcl-2* have been studied in various types of cancers but their relationship to growth factors, especially to gastrin, HGF, TGF and gastrin, have not been thoroughly examined in gastric cancer tissue, cancer margin or intact normal mucosa.

According to our experience, Bcl-2, unlike Bax, which was detected only in about 56% of GC, but has been found in all cancer samples (100%), in 80% of cancer margin and in 64% of normal tissue samples. The *bcl-2* expression in GC was higher

than that of *bax*, and the calculated *bax/bcl-2* ratio was several times lower in the cancer than in cancer margin or in adjacent normal mucosa (Fig. 10). Unlike the intact gastric mucosa, in which no protein expression for HGF and Bax was found and Bcl-2 was only weakly expressed, the biopsy specimen taken from gastric cancer, showed increased expression of HGF and TGFα in about 35% of cases. In summary, we found that patients infected with *H. pylori* - CagA-positive strains, are at a higher risk of developing GC. We also confirmed that the increased production of gastrin [19] and the over-expression of growth factors such as HGF and TGFα [48, 49] contribute to gastric carcinogenesis. Finally, in GC, the dysregulation of the Bax/Bcl-2 system was noticed with a significant down-regulation of proapoptotic Bax.

Cancerogenesis results from uncontrolled cell proliferation and an increase in the number of cells with mutated genes with genome instability and the appearance of cell subpopulation with altered chromosomes. Initially the tumor growth may be local so called *carcinoma in situ* but then the neoplastic cells loose their contact with basal membrane (due to activity of collagenase IV) and infiltrate the neighboring tissues. This uncontrolled cell proliferation is accompanied by the inhibition of apoptosis, which normally is the only way of removal of damaged or unnecessary cells. Several protooncogenes participate in this process such as C--Myc stimulating both apoptosis and cell proliferation, p53 that normally serves as genome guardian and repairs DNA but when mutated it stops to repair DNA resulting in the inhibition of apoptosis and increase in cell survival and in effect in increase of tumor size.

Scheme proposing a key role of gastrin in gastric cancerogenesis is presented on Fig. 7. Point mutation of K-ras which can occur randomly in gastric mucosa exposed to the influence of *H. pylori* and its products lead to cascade of events. Oncogenic mutation occurring in K-ras results in its elevated intracellular activity causing overexpression of gastrin and other growth factors like TGFα, HGF and EGF [50,51]. Furthermore cytotoxic products of *H. pylori* evoke activation of NF-κ-B-dependent cytokines IL-8, TNFα [52,53]. Elevated level of those cytokines adds to overexpression of gastrin gene. Gastrin as a potent mitogen using MAP-kinases and C-jun amino-terminal kinase signal transduction pathway promotes growth and cell division dependent on c-fos and c-jun activity [54,55]. Moreover, gastrin is able to activate p53 gene expression without activation of cell cycle inhibitors (p21) [56]. This can lead to cell cycle dysregulation which with already activated mitogenic activity can result in

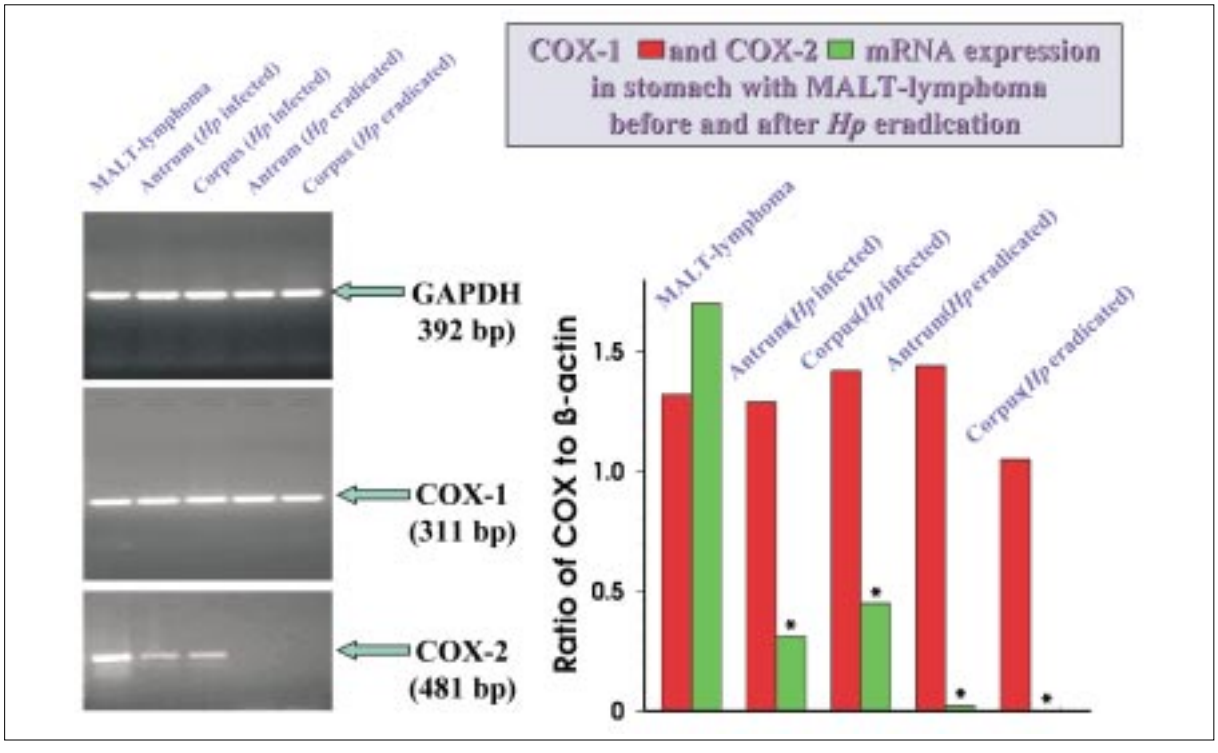

Figure 11. Expression of COX-1 and COX-2 in MALT-lymphoma, antrum and corpus of stomach before and after *H. pylori* eradication.

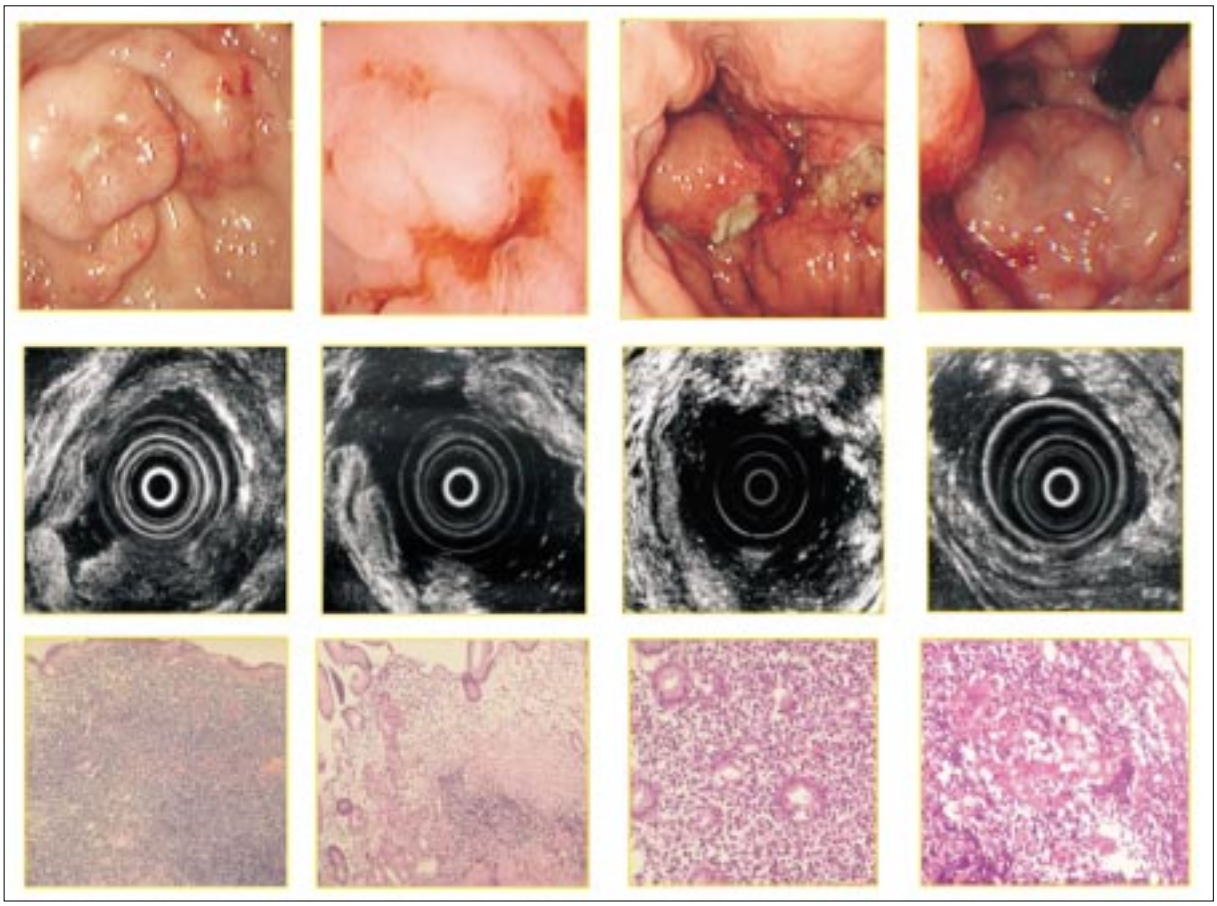

Figure 12. Typical endoscopic, endosonographic and histolkogical pictures in MALT-lymphoma patients used in our study [20,60].

abnormal hyperproliferation of epithelial cells and finally gastric cancer formation.

Tumor growth (steps 3 in cancerogenesis) that results from the proliferation of cancerous cells requires increased supply of nutrients and oxygen through the excessive growth of new vessels in **tumor – angiogenesis (step 4 in cancerogenesis).** This process is determined mainly by the induction of COX--2, a rate-limiting enzyme in prostaglandin (PG) biosynthesis [57,58], possibly due to the action of potent mitogens such as gastrin and growth factor (TGFα, HGF) generated in the tumor tissue [19,20, 35,59,60]. COX-2 in turn stimulates the release of PG and angiogenic substances such as VEGF, bFGF, and angiopoetins. Such overexpression of COX-2 has been detected in the *H. pylori* infected gastric mucosa and this was further enhanced in the tumor tissue [57–59]. After eradication of *H. pylori*, the expression of COX-2 disappeared from previous site of MALT tumor and significantly fell in infected *antrum* and corpus mucosa (Fig. 11). Following pretreatment with Vioxx and inhibition of COX-2, the expression of this enzyme was enhanced, thus reinforcing the suggestion that the selective inhibition of COX-2 may provide a chemopreventive effect against gastric cancerogenesis [60].

The treatment at the step 3 of cancerogenesis includes the administration of specific COX-2 blockers (such as Vioxx or Celecoxib) that are expected to reduce the angiogenesis, resulting in the attenuation of tumor growth.

Association of *H. pylori* andf MALT-lymphoma. Involvement of gastrin and cyclooxygenase-2

Gastric lymphomas are the commonest of the extranodal lymphomas but they comprise less than 5% of all gastric cancers [60]. The gastric lymphoma show characteristic features closely related to the structure and function of gastric mucosa so called MALT (Mucosa Associated Lymphoid Tissue) and appear to be evolved to protect the mucosa directly exposed to antigens in gastric environment such as the presence of *H. pylori* (Fig. 12). Normally there is no lymphoid tissue in the stomach, but the appearance of such

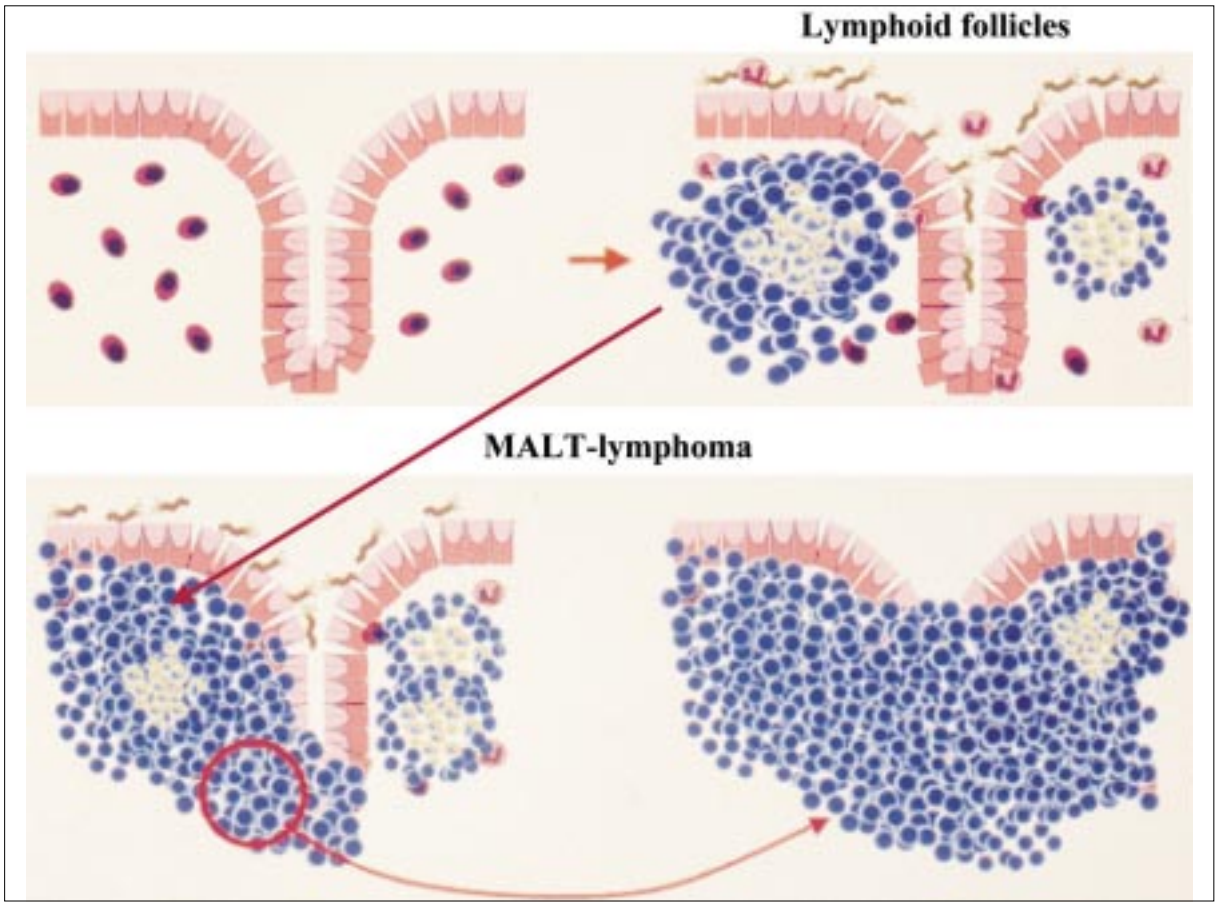

Figure 13. Schematic presentation of development of lymphoid follicles and MALT lymphoma in *H. pylori* infected stomach (Genta et al, 2000).

follicules in the gastric mucosa is virtually pathognomonic to *H. pylori* infection (Fig. 13).

There are several independent sources of evidence that link prior *H. pylori* infection with MALT-lymphoma [60–66] including; 1. The presence of *H. pylori* can be detected in more than 90% of cases of MALT-lymphoma (Fig. 14); 2) Eradication of *H. pylori* leads to the resolution of low-grade MALT lymphoma with over 70% of cases in stage IE of MALT-lymphoma regressing almost completely following successful anti-*H. pylori* therapy (Fig. 15); 3) despite of the composition of the MALT-lymphoma tumors consisting predominantly with B lymphocytes, a marked increase of gastrin has been noticed both in the gastric lumen and the plasma similar to that observed in *H. pylori* infected GC patients and accompanied by the marked increment in plasma levels of cytokines (IL-1, IL-8 and TNFα) that could contribute to the stimulation of gastrin release; 4. The source of this gastrin has not been fully established but the fact that the lymphoma tissue contained several times higher level of gastrin than the intact gastric mucosa and the finding of the detection of gene expression in this tissue of both gastrin receptors (CCK_B) and gastrin itself is in keeping with our hypothesis that the lymphocytes B overexpress gastrin and its receptors that are involved in the MALT-lymphoma growth. Our *in vitro* studies with lymphoblasts support the overall role of gastrin and cytokines in the pathogenesis of MALT--lymphoma.

Fig. 16 shows schematically the proposed pathomechanism of MALT-lymphoma based on our findings obtained from the limphoid cells emphasizing central role of gastrin in its development. In *H. pylori* infected stomach several processes including apoptosis, hyperproliferation of epithelial cells and infiltration of macrophages (Mf) and monocytes (Mo) can occur. Elevation of gastrin (presumably originating from the lymphocytes) during infection as well as an increased expression and synthesis of proinflammatory and chemoatractive cytokines (IL--1, IL-6, IL-7, IL-8, IL-15) evoke local immune response and clonal activation of T lymphocytes (LyT) sensitized by specialized antigen presenting cells (APC), followed by B cells (LyB) activation and

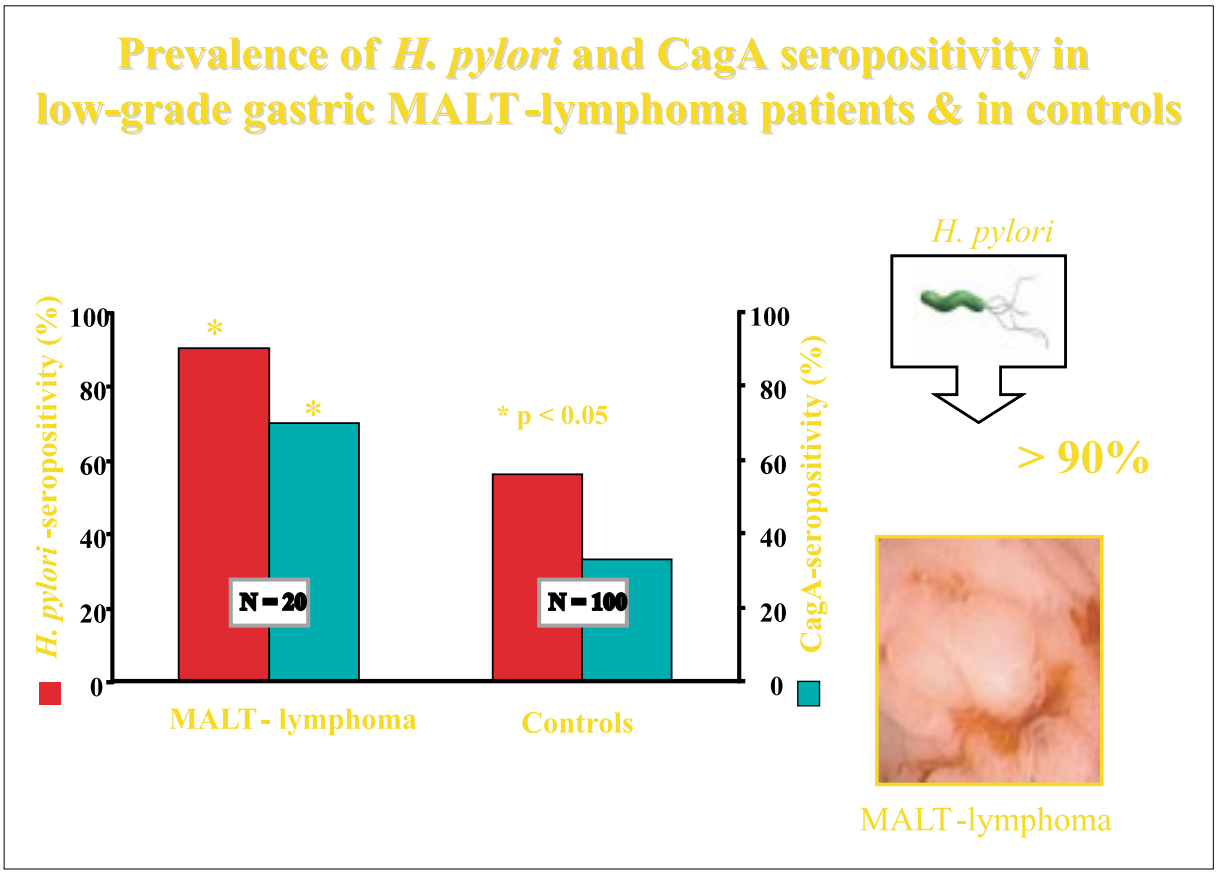

Figure 14. Seroprevalence of *H. pylori* IgG and Cag A in MALT-lymphoma (on left) and the endoscopic picture of MALT-lymphoma tumor (on right).

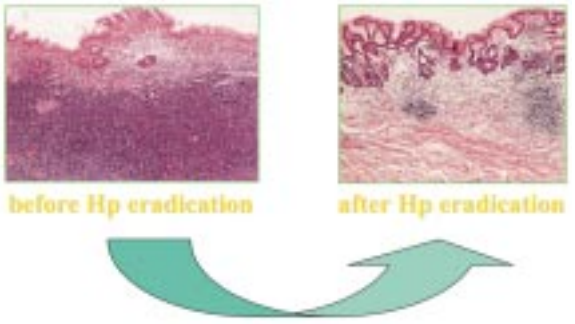

Figure 15. *H. pylori* eradication therapy leads to almost complete regression of MALT lymphoma tumors.

excessive proliferation. In this model MALT lymphoma formation can be considered as an abnormal immune response to *H. pylori* infection. Gastrin acts as a trophic hormon not only for gastric mucosa but also for B lymphocytes excessively proliferating from lymphoid follicle and penetrating gastric mucosa.

The possibility of cure of gastric MALT-lymphoma using an anti-*H. pylori* therapy is an excellent example of the susceptibility of the *H. pylori* -induced gastric tumor (as well as gastroduodenal ulceration) to the treatment and cure by eradication of the germ from the stomach (Fig. 17). Although Genta et al. [64] showed that the eradication of *H. pylori* is followed by reduced, although not complete disappearance of lymphoid follicles in the gastric mucosa, the data obtained from various oncology centers provide strong circumstantial evidence in support of the pathological role played by *H. pylori* infection in the pathogenesis of gastric MALT-lymphoma and has led to inclusion of this tumors as an indication for treatment in all *H. pylori* Consensus Conferences held to date in USA or Europe [65,66]. Figure 17 illustrates that dominant feature of *H. pylori* infection is greatly enhanced plasma gastrin level, independent on the intragastric pH. These secretory disorders may result either in duodenal ulcer when infection dominates in antrum or gastric ulcer, MALT-lymphoma or cancer when infection is confined to the corpus mucosa.

It is of interest that MALT-lymphoma, similarly to adenocarcinoma, expresses COX-2 and generates excessive amounts of PG that could be responsible

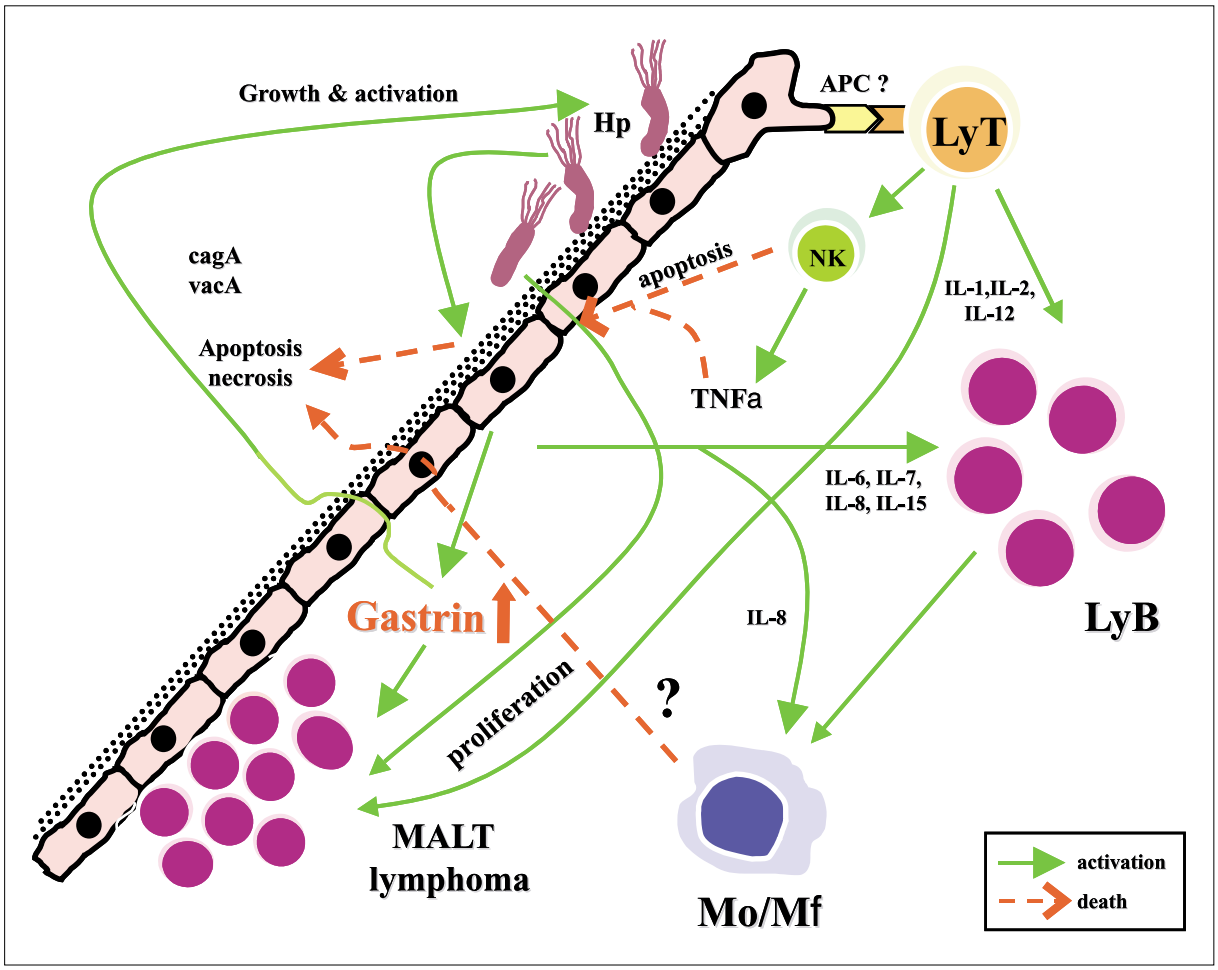

Figure 16. Schematic presentation of pathomechanism of *H. pylori* induced MALT-lymphoma with central role of gastrin and growth factors.

for the lymphocyte B proliferation, the decrease in apoptosis, the mutagenesis and the angiogenesis. Following the *H. pylori* eradication, there was not only the regression of the tumor but also an immediate fall in gastrin release followed by reduction in COX-2 expression. Thus, similar molecular changes appear to operate in MALT-lymphoma as in GC, indicating that there is a common pathomechanism underlying the apparently different disorders, gastric cancerogenesis and the MALT-lymphoma [67].

CONCLUSIONS

1. The infection with *H. pylori*, especially expressing CagA, is significantly higher in gastric cancer and occurs in almost all MALT-lymphoma patients, playing a crucial role in gastric cancerogenesis;

2. The major morphological events in gastric cancerogenesis is the development of atrophic gastritis passing in cascade to intestinal metaplasia and dysplasia followed by the transformation of normal mucosal cells into malignant cells, at first developing locally but then infiltrating neighboring tissues and finally spreading *via* blood or lymph vessels to lymph nodes and distant organs.

3. MALT-lymphoma shows different morphological feature with predominant formation of lymphoid follicules in the mucosa and then excessively infiltration and destruction of the surface epithelium followed by slow infiltration of neighboring tissues and lymphnodes;

4. The molecular pathomechanism of gastric adenocarcinoma and MALT-lymphoma basically has common features including an upregulation of gastrin and its receptors, that in combination with other growth factors (HGF, TGFα and EGF) seem to act as cancerogens, playing a crucial role in the transformation of normal mucosal cells

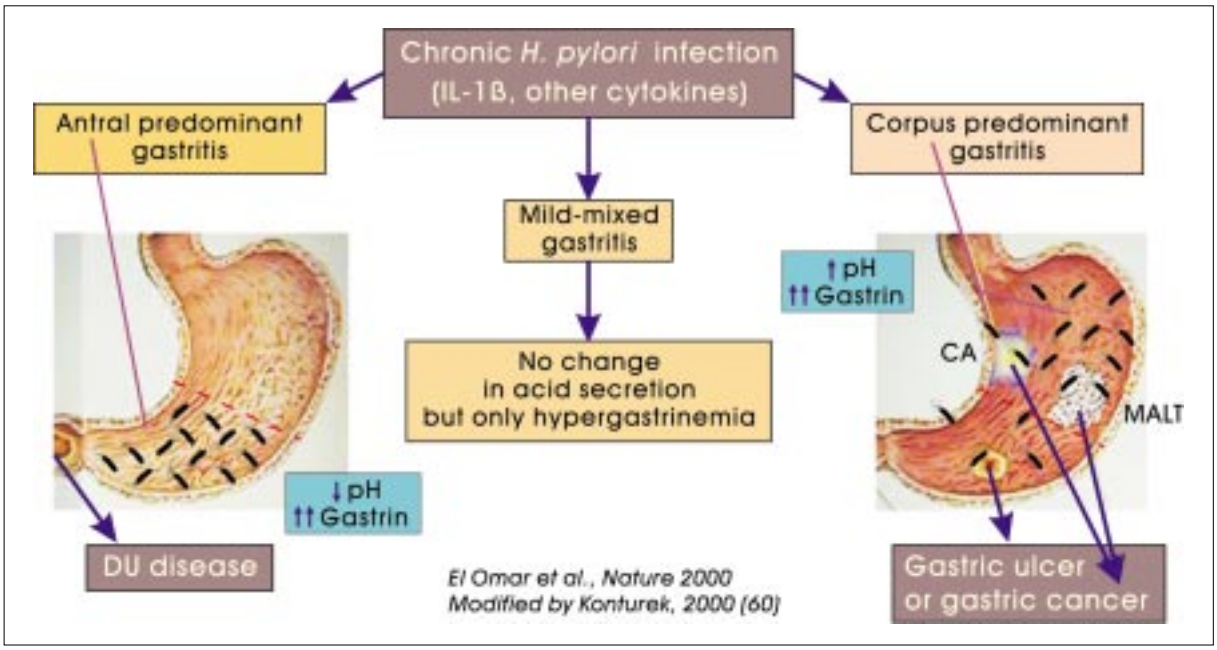

Figure 17. The localization of *H. pylori* infection in the stomach determines whether gastric hypesecretion with duodenal ulcer (antral prevalent infection) develops or whether gastric hyposecretion, hypochlorhydria and gastric ulcer, gastric carcinoma or MALT lymphoma (corpus prevalent infection) develop. Note that *H. pylori* effects depend upon the localization of infection, always resulting in an increase in gastrin release. Eradication of *H. pylori* cures gastritis, gastroduodenal ulcerations and MALT lymphoma but fails to control gastric cancer.

or lymphocytes into the malignant cells through the mutation of several protooncogenes such as C--myc, K-ras, C-fos etc. that are responsible for the increased proliferation and spreading of these cells;

5. Both gastric cancer and MALT-lymphoma show overexpression of COX-2 probably induced by gastrin and other growth factors and appear to contribute to angiogenesis in growing tumor *via* production of PG, bFGF, VEGF, angiopoetins etc.

6. The major difference between gastric adenocarcinoma and MALT-lymphoma is that eradication of *H. pylori* causes almost complete regression and cure of MALT lymphoma, whereas such eradication in gastric cancer, though recommended, is probably successful only in precancerous state but not in fully developed cancer.

7. Based of the results of these studies we postulate the nation-wide periodic screening of patients, especially closest family members of gastric cancer patients or those showing history of gastrectomy, repeated gastric ulcer or chronic atrophic gastritis.

8. The research on uncontrolled growth and proliferation of cancer cells emphasizes the important role of growth factors, their receptors at the cancer cell membrane and intracellular enzymatic pathways. The preliminary results with anti-growth agents inactivating the growth factors, their receptors, intracellular signaling systems or the angiogenesis seem to be the most promising anti-cancer remedies.

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